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BPSI Holdings Inc.,
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Patents ADP number *(if you know it)* 6859060001

If the applicant is a corporate body, give the country/state of its incorporation Delaware, USA

4. Title of the invention Method and Apparatus for the Coating of Substrates for Pharmaceutical Use

5. Name of your agent *(if you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

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Date 13th November 1996

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Method and Apparatus for the Coating of Substrates for Pharmaceutical Use

The present invention relates to methods of coating substrates, to apparatus for coating substrates and to coated substrates for pharmaceutical use. In particular, but not exclusively, the invention relates to the coating of pharmaceutical substrates to produce solid dosage forms.

It is to be understood that the term "solid dosage form" is to be interpreted in a broad sense as covering a wide variety of pharmaceutical products. Thus the term covers pharmaceutical products to be taken orally, for example, pharmaceutical tablets of conventional shape as well as capsules and spherules and tablets of unconventional shape. The term also covers pharmaceutical products not taken orally, for example, a pessary, a bougie, a suppository or a patch for application to the skin. Also, where reference is made to "pharmaceutical substrate" it is to be understood that the term covers the substrates of the solid dosage forms indicated above. The term "solid dosage form" does not, however, include pharmaceutical products such as small pellets and granules, for example small pellets which are filled into capsule shells for administration and granules which are compressed to form tablets.

The invention is of particular application to pharmaceutical tablets of conventional shape. Where

reference is made throughout the specification to pharmaceutical tablets, it should be understood that this should be interpreted in a broad sense, unless it is clear to the contrary, as covering also other pharmaceutical products taken orally, for example capsules and spherules.

It will be understood that the term "active material" and "active component" used throughout the specification includes material which is biologically active and will comprise one or a mixture of pharmaceutical materials. The pharmaceutical materials include those materials which are administered for the prevention and/or treatment of disease.

In a conventional method of producing a pharmaceutical tablet, a mixture containing the biologically active ingredient together with diluents such as lactose and other ingredients is mixed and portions of the mixture are formed into discrete tablets by, for example, pressing samples of the mixture.

The resulting tablet core may be coated using, for example, a conventional liquid coating technique in which the tablet cores are tumbled in a drum while liquid coating material is sprayed onto the surfaces of the tablet cores. The liquid coating on the surfaces of the cores is usually dried by heating to dry the coating.

A problem with the method of producing tablets described above is that, due to inhomogeneity of the mixture from which the tablet cores are made, the amount

of active ingredient in the resulting tablet cores varies from one tablet to the next. While that is a problem for all types of tablet core produced in that way, it is a particularly serious problem when the amount of active ingredient in each core is low, for example for active compounds of high activity. In that case a small absolute variation in the percentage amount of active ingredient in the cores corresponds to a significant variation in the dose contained in each tablet which is clearly most undesirable.

Various solutions to that problem have been proposed.

In one method, the active ingredient and a small amount of diluent are granulated together and the granulated mixture is added to further diluent. The mixture is then compressed in the usual way to form tablet cores. Using that method, at each stage the proportion of active ingredient added to the diluent is high thus helping to reduce the variation in the dose in each tablet core. However, the variation in the dose for tablets formed by this method is still found to be as much as ± 15%.

In an alternative known method, a two-layer tablet core is produced by compressing a powder having a lower layer of diluent and an upper layer of diluent mixed with the active ingredient. Cores formed by this method, however, require special designs of presses and are found to have a relatively large variation in their contained

dose. They also require reformulation of the components making up the core. Also, such presses generally have lower rates of production of cores than standard presses.

In another known method, a coating solution containing active material is applied to the surfaces of small beads using conventional spray coating techniques, for example by spraying the coating solution towards the beads as they are tumbled in a revolving drum. The coated beads are filled into capsule shells for administration. Such a method is not appropriate for use where accuracy in the amount of the active material applied to the cores is required because there is little control over the amount of coating material applied to each core using that method.

It is an object of a first aspect of the invention to overcome or mitigate one or more of the above mentioned disadvantages.

According to the first aspect of the invention, there is provided a method of coating a pharmaceutical substrate, the method including the steps of:

(a) applying an active coating material to a surface of the substrate to form an active coating layer, the active coating material comprising biologically active material and

(b) applying a cover coating material onto the active coating layer to form a cover coating layer such that the active coating layer is substantially completely covered by the cover coating layer.

Thus biologically active material is applied to the outer surface of the substrate. In the case of pharmaceutical tablets, active material is applied to an outer surface of a preformed pharmaceutical tablet core. The active coating material may therefore be applied to the substrate in a small quantity and thus the percentage of biologically active component in the active coating material mixture may be high, leading to less variation in the amount of active material from one dosage form to the next compared with the known methods described above.

The active coating material may be applied to a substrate which contains no biologically active material or may be applied to a substrate which contains the same or a different biologically active material. Thus the method may be used to provide a solid dosage form which contains one active component in the substrate and a different active component as a coating on the surface of the substrate. It is envisaged that those active components could be released at different rates.

Where the material containing active components is applied to the outer surfaces of a pharmaceutical substrate as a coating, the layer containing the active components will be susceptible to damage resulting in loss of active material. By applying cover coating over the surface of the active coating layer the active coating layer is protected from damage. That protection is especially desirable when the coating material contains a small amount of active component. In addition

to protection from physical damage, the coating may also provide protection from chemical damage; for example, the cover coating may be moisture resistant and/or may give delayed release of the active components.

It is clearly preferable for the cover coating to cover completely all of the active coating but incomplete coating, for example at the edge of the active coating layer, may be tolerated in some circumstances.

While the cover coating will often comprise a single coating of one material composition, it may comprise more than one coating and/or coatings including more than one composition.

Preferably, the active coating material is applied electrostatically. There are various advantages in applying coating materials electrostatically, for example, reduction in waste of coating material, improved coating efficiency and improved coating weight uniformity.

In one alternative of the first aspect of the invention, the active coating material is applied in the form of a dry powder.

Advantageously, at least 90% by weight of the particles of the active coating material have a particle size between from 1 to 200μm. Preferably, at least 90% by weight of the particles of the active coating material have a particle size between from 1μm to 100μm. The term "particle size" refers to the equivalent particle diameter of the particles and may be measured using, for

example, laser light diffraction. The particle size of the powder is an important factor in powder coating techniques. If the particles of the powder are very small, the powder will often be too cohesive for successful powder application using many powder coating techniques. However, large particles can be disadvantageous because they are often more difficult to coat onto a surface and, if the coating material is to be fused after application to the surface, longer fusing times may be required, leading to increased risk of damage to the substrate and to the active component.

Alternatively, the coating material may be applied in the form of a liquid.

Advantageously, the active coating material further includes one or more excipients. The formulation will usually consist of the active component and a mixture of excipients that will aid in the coating of the material. The formulation may also include other components, for example, colorants and/or flavourings and/or agents to control the rate of release of the active component.

Advantageously, the substrate is supported on a support means during the coating of the active coating material. This is particularly advantageous where the substrate is fragile, for example a tablet core, because the likelihood of damage to the substrate is reduced. Supporting of the substrate also allows the application of the coating material to be more accurate and the uniformity of coating can be improved compared with the

case in which the substrate is, for example, tumbled in a revolving drum during the coating stage, as is conventional practice for the coating of tablet cores.

Advantageously, the support means conveys the substrate through a region adjacent to a source of the active coating material. That allows the method to be continuous.

In one advantageous embodiment of the first aspect of the invention, the method comprises supporting the substrate adjacent to the source of the active coating material with a surface of the substrate maintained at such a different electric potential from that of the active coating material that the application of the electric potential causes the active coating material to move from the source of the active coating material towards the substrate, a surface of the substrate becoming coated with the active coating material.

Preferably, the substrate is supported from above and the powder moves from the source upwards towards a lower surface of the substrate.

Preferably, the substrate is charged when the substrate is adjacent the source of the active coating material. Alternatively, or in addition, the source of active coating material may be charged.

The method may further include the step that after the active coating layer is applied the active coating material is treated to form an active film coating secured to the surface of the substrate. Where the

coating material is in the form of a powder material, the treatment advantageously comprises a heating step, preferably by infra red radiation, but other forms of electromagnetic radiation may be used. Usually, the change in the coating upon heating will simply be a physical change from a powder to a liquid and then, on cooling, to a solid coating, but there are other possibilities: for example, the powder coating may comprise a polymer which is cured during the treatment step, for example by irradiation with energy in the gamma, ultra violet or radio frequency bands, to form a cross-linked polymer coating.

Alternatively, the active coating material applied to the surface of the substrate might not be treated to form an active film coating. A cover coating applied subsequently over the active coating material could be used to seal the active coating on the surface of the substrate.

Where the coating material is in the form of a liquid, the treatment advantageously comprises drying the coating material with a heater although other methods could be used.

The coating material containing the active component is susceptible to damage at high temperatures and it is therefore particularly important that the temperature of treatment is not high. Advantageously, the temperature of treatment is less than 250°C, preferably less than 200°C and more preferably less than 150°C. Where the

higher treatment temperatures are used, the duration of the treatment is advantageously short to reduce the possibility of damage of the coating material.

Preferably, the cover coating material is applied electrostatically. The cover coating material may be in the form of a powder. The cover coating material may also include active material. The active material in the cover coating may be the same or different from the active material in the active coating layer.

Advantageously, at least 90% by weight of the particles of the cover coating material have a particle size between from 1 to 200μm.

Advantageously, the substrate is supported on a support means during the coating of the cover coating material. As indicated above, that reduces the risk of damage of the substrate and can increase the accuracy of the application of the coating.

Preferably, the support means conveys the substrate through a region adjacent to a source of the cover coating material.

In one advantageous embodiment of the invention, the method comprises supporting the substrate adjacent to the source of the cover coating material with a surface of the substrate maintained at such a different electric potential from that of the cover coating material that the application of the electric potential causes the cover coating material to move from the source of the cover coating material towards the substrate, a surface

of the substrate becoming coated with the cover coating material.

Advantageously, the substrate is supported from above and the powder moves from the source upwards towards a lower surface of the substrate.

Preferably, the substrate is charged when the substrate is adjacent to the source of the cover coating material. Alternatively, or in addition, the source of cover coating material may be charged.

Advantageously, the method further includes the step that after the cover coating layer is applied the cover coating material is treated to form a film coating secured to the surface of the substrate. The treatment of the cover coating layer may be similar to that of the active coating layer described above.

In a preferred embodiment of the first aspect of the invention the active coating layer covers only part of a surface of the substrate. In that embodiment, the cover coating layer may cover only part of a surface of the substrate.

The method may further include the step of applying a further coating material to a surface of the substrate to form a further coating layer. The further coating material may include biologically active material, the further coating layer forming a further active coating layer and the method may further include the step of applying a further cover coating material onto the further active coating layer to form a further cover

coating layer such that the further active coating layer is substantially completely covered by the further cover coating layer.

Thus substrates having two or more different active components may be produced. The cover coating material covering the first active coating may be different from that covering the second active coating so that the rate of release of the first active component may be different from that of the second active component. Alternatively, the two active components may be the same and the cover coatings may be the same or different materials. One or more of the cover coating materials may contain active material.

Advantageously, the method is continuous. In practice, there are considerable advantages in being able to operate the coating process continuously rather than as a batch process.

Advantageously, the coated pharmaceutical substrate is a solid dosage form, preferably a solid dosage form for oral administration.

The quantity of active coating material in the active coating layer may be substantially equal to a dose of the active material, or a fraction of the dose, for example $^1/_2$ or $^1/_3$ of a dose of the active material. It will be understood that the quantity of active material will depend on the active component used and the number of solid dosage forms to be taken by the patient for each dose. Where more than one layer of the active coating

material is to be applied to each substrate, the quantity of active component in each layer will be chosen accordingly.

The first aspect of the invention also provides apparatus for coating a pharmaceutical substrate according to a method as described above.

The first aspect of the invention also provides an apparatus for coating a pharmaceutical substrate, the apparatus comprising:

(a) a source of active coating material,

(b) support means for supporting a substrate adjacent to the source of the active coating material such that the active coating material forms an active coating layer on a surface of the substrate,

(c) a source of a cover coating material,

(d) means for conveying the substrate having the active coating layer to a position adjacent to the source of cover coating material such that the cover coating material forms a cover coating layer which substantially completely covers the active coating layer.

The apparatus advantageously includes means for applying the active coating material and/or the cover coating material electrostatically. As indicated above, the coating material may be applied in the form of a dry powder or in the form of a liquid.

Advantageously, the source of active coating material comprises a conveyor for conveying active coating material through a region in which the substrate

is supported by the support means.

The conveyor may comprise a conveyor belt. Where the conveyor is used it is possible to provide a substantially uniform supply of coating material to the region in which the coating is applied.

Advantageously the apparatus further includes means for supplying active coating material to the source, comprising a reservoir of active coating material arranged adjacent to the conveyor, and means for transferring the active coating material from the reservoir to the conveyor. The rate of transfer of the coating material from the reservoir to the conveyor can be adjusted to change the amount of coating material applied to the substrate.

Advantageously, the means for transferring the active coating material includes charging means for applying a charge to the conveyor. The charge may be applied using a corona charge wire adjacent to the conveyor. The charged conveyor attracts coating material from the reservoir onto the surface of the conveyor from where it is conveyed to the region in which the coating is applied. Thus it is possible to obtain a very thin uniform layer of coating material on the conveyor surface.

Preferably, the reservoir is arranged below the conveyor.

According to the first aspect of the invention, there is also provided, a pharmaceutical product comprising a substrate, an active coating layer on a

surface of the substrate, the active coating layer comprising biologically active material, and a cover coating layer substantially completely covering the active coating layer.

The pharmaceutical product may further include a second active coating layer, and a cover coating layer substantially completely covering the second active coating layer. In the case of a tablet, for example, the first active coating layer may cover one face of the tablet and the second active coating layer may cover the opposite face of the tablet.

The cover coating layer covering the first active coating layer may be different from the cover coating layer covering the second active coating layer. Thus different release rates of the two active coatings may be obtained as described above.

Advantageously, the coated pharmaceutical product is a solid dosage form, preferably a solid dosage form to be administered orally.

The substrate may contain biologically active material. As indicated above, the method according to the invention is particularly suitable for the case in which the quantity of active component to be administered is low. Where a large quantity of a first active component is to be co-administered with a small quantity of a second active component, the first active component may be present in the substrate, for example the tablet core, in the usual way and the second active component

may be contained in a coating on the surface of the substrate in accordance with the present invention.

The first aspect of the invention also provides a pharmaceutical product made by a method described above.

In accordance with a second aspect of the present invention, there is provided a method of coating a pharmaceutical substrate, the method including the step of applying a metered dose of an active coating material to a surface of the substrate, to form an active coating layer on the surface, the active coating material comprising biologically active material.

In conventional coating methods, the part to be coated, for example, a pharmaceutical tablet core, is tumbled in a revolving drum while coating material is sprayed into the drum such that coating material is applied to all of the surfaces of the cores. It has been proposed that the substrate may be supported on a surface while coating material is sprayed towards exposed surfaces of the substrate. A problem with such methods is that there is a large variation in the amount of coating material applied to each core. While that can be tolerated where the coating is, for example, a cosmetic coat, where the coating material contains active material, very accurate application of the coating material on each surface is required.

In a method according to the second aspect of the invention, a metered dose of coating material is applied to each substrate, thus allowing for the application of

the required amount of active material to each substrate. This is to be contrasted with the known methods where coating material is sprayed towards the cores. In that case the amount of coating material applied to each substrate depends on many factors all of which would require close control if accurate application is to be achieved. It will be understood that whilst reference is made to applying a metered dose, that should not be taken to imply that there is necessarily any measurement of the amount of material applied.

Advantageously, the active coating material is applied in the form of a liquid. Thus a metered volume of liquid may be applied to each substrate.

Advantageously, a predetermined number of droplets of active coating material are applied to the surface of the substrate. Thus where the droplets are of the same size, the number of droplets applied to the substrate surface determines the amount of active material applied. By altering the number of droplets applied, the apparatus use can easily be adapted to apply the required quantity of active material.

The second aspect of the invention also provides a method of coating a pharmaceutical substrate, the method including the step of applying a quantity of an active coating material to a surface of each substrate, to form an active coating layer, the active coating material including biologically active material, the method being such that the coefficient of variation of the quantity applied to each substrate is not more than 15%.

As indicated above, where the coating material includes active material, the accuracy and reproducibility of the application of the material to the substrates is of particular importance. For known spraying techniques such as those described above, the coefficient of variation can be 50% or more. Whilst that is acceptable where the coating is a cosmetic coating, it is not acceptable where the coating contains active material. Preferably the coefficient of variation is not more than 10%, and most preferably 3% or less.

The second aspect of the invention further provides a method of coating a pharmaceutical substrate, the method including the step of applying active coating material from a supply to a surface of the substrate to form an active coating layer, the active material comprising biologically active material, wherein the active coating material is applied in the form of individual liquid droplets which are propelled from the supply directly towards a surface of the substrate.

As indicated above, where the material is applied as a plurality of individual droplets, it is more simple to alter the dose of active material applied to the substrate by changing the number of droplet applied. Thus advantageously, the number of droplets applied is controllable.

The second aspect of the invention provides the use of an ink jet head in the coating of pharmaceutical substrates with active coating material, the active

coating material comprising biologically active material. A conventional ink jet head, for example those used for ink jet printers, can be used to apply an easily controllable amount of material from the head onto a substrate.

In accordance with a second aspect of the present invention, there is also provided, a method of coating a pharmaceutical substrate, the method including the step of applying an active coating material to a surface of the substrate to form a coating layer, the active coating material comprising biologically active material, in which the area of the surface of the substrate covered by the active coating layer is less than 40% of the total surface area of the substrate. Advantageously, the area covered by the active coating layer is less than 25% of the total surface area of the substrate.

The second aspect of the present invention further provides a method of coating a pharmaceutical substrate, the method including the step of applying an active coating material to an exposed surface of the substrate to form an active coating layer, the active coating material comprising biologically active material, in which the active coating layer covers only a part of the exposed surface of the substrate.

Where the quantity of active material to be administered using each solid dose is small, as indicated above, it is advantageous for the proportion of active component in the active coating material to be large.

In conventional coating methods the part to be coated, for example a pharmaceutical tablet core, is tumbled in a revolving drum during the coating process such that coating material is applied to all of the surfaces of the core. It has also been proposed that the substrate may be supported on a surface while coating material is applied to exposed surfaces of the substrate. In that method, approximately half of the surface of the substrate becomes coated with the coating material.

By using the method of the second aspect of the invention, a smaller proportion of the surface of the substrate is covered and therefore a smaller amount of coating material may be used. Thus the proportion of active component in the coating material is increased.

Another problem with the known methods described above is that there is overspray of coating material which has to be discarded or recycled. That would be particularly disadvantageous in a method according to the present invention in which the coating material contains an active component.

In the method according to the second aspect of the invention, coating material may be applied accurately to a predetermined part of the substrate, thereby helping to reduce loss of powder due to overspray.

Advantageously, the area of the surface covered by the active coating layer is less than 25%, preferably less than 10% of the total area of the surface. Preferably, the coated area is less than 5% of the total

area. The active coating material may be applied to the surface of the substrate in the form of a small spot.

Advantageously, the coating material is applied in the form of a jet of liquid droplets directed at an exposed surface of the substrate. Whereas known spray devices for use in coating processes spray a wide area with coating material, a jet of liquid droplets allows material to be applied more accurately with less over-spray.

Advantageously, the coated pharmaceutical substrate is a solid dosage form.

The active coating material may be applied electrostatically.

Advantageously, the methods of the second aspect of the invention further include the step of applying cover coating material to the surface of the substrate to form a cover coating layer such that the active coating layer is substantially completely covered by the cover coating layer. The advantages of a cover coating layer are indicated above in respect of the first aspect of the invention.

According to the second aspect of the invention, there is provided, a method of coating a pharmaceutical substrate, the method including the step of applying an active coating material to a surface of the substrate to form an active coating layer, the active coating material comprising biologically active material, the active coating material being applied in the form of a jet of

liquid droplets of active coating material.

The second aspect of the invention also provides an apparatus for coating a pharmaceutical substrate, the apparatus comprising

(a) a source of active coating material, the active coating material comprising biologically active material,

(b) support means for supporting the substrate adjacent the source of active coating material

wherein the source comprises means for applying a metered dose of active coating material on a surface of the substrate.

Also provided is an apparatus for coating a pharmaceutical substrate, the apparatus comprising

(a) a source of active coating material, the active coating material comprising biologically active material,

(b) support means for supporting the substrate adjacent the source of active coating material

wherein the source comprises an ink jet head.

Furthermore, the invention provides an apparatus for coating a pharmaceutical substrate, the apparatus comprising

(a) a source of active coating material, the active coating material comprising biologically active material,

(b) support means for supporting the substrate adjacent the source of active coating material

wherein the source comprises means for directing droplets of liquid active coating material towards a surface of the substrate.

The second aspect of the invention further provides, an apparatus for coating a pharmaceutical substrate, the apparatus comprising

(a) a source of active coating material, the active coating material comprising biologically active material

(b) support means for supporting the substrate adjacent the source of active coating material

(c) means for applying active coating material from the source onto a surface of the substrate to form a layer of coating material on the surface of the substrate such that the area of the surface covered by the coating layer is less than 25% of the total surface area of the substrate.

Advantageously, the means for applying the coating material includes means for directing coating material towards the surface of the substrate in the form of a jet of liquid droplets. The means for forming a jet of liquid droplets may be similar to devices known in the field of ink jet printing heads for directing liquid droplets of ink towards a printing surface.

Advantageously, the apparatus further includes means for applying a cover coating material onto the surface of the substrate to form a cover coating layer such that the cover coating material layer substantially completely

covers the active coating layer.

The second aspect of the invention also provides a pharmaceutical solid dosage form comprising a substrate and an active coating layer covering less than 25% of the surface area of the substrate the active coating layer comprising biologically active material. Advantageously, where the substrate is a tablet core, the active coating layer covers less than the total area of a face of the core.

Preferably the area covered by the active coating material layer is less than 20%, more preferably less than 10%. In one preferred embodiment of the invention, the coating material layer is in the form of a spot of material on the surface of the substrate.

The coating layer may be shaped, for example to form a pattern, a picture, symbols, letters or numerals.

The solid dosage form advantageously further comprises a cover coating layer substantially completely covering the active coating layer.

The second aspect of the invention further provides a pharmaceutical solid dosage form made by a method described above.

It will be understood that the method according to the second aspect of the invention could include a combination of the features described above in respect of the second aspect of the invention and may include features of the method described above in respect of the first aspect of the invention. Furthermore, the method

of the first aspect of the invention may also include features described above in respect of the second aspect of the invention.

In accordance with a third aspect of the invention, there is provided a method of coating a substrate, the method including the steps of applying an active coating material to a surface of the substrate to form an active coating layer, the active coating material comprising biologically active material, wherein the active coating layer is removable from the substrate.

Active components are often administered in tablet form. As indicated above, conventional tablets include a small amount of active component and a large amount of diluent such as lactose so that the tablet is a convenient size. The tablet is a convenient way for the active component to be administered because each tablet contains a predetermined metered dose of the active material.

However, some patients find the taking of tablets difficult, for example because of their size or because of the presence of the other ingredients in the tablet composition.

In accordance with the third aspect of the invention, the active material is applied as a coating to a substrate from which it can be removed.

In one alternative embodiment of the third aspect of the invention, the coating material is applied directly onto a surface of the coating apparatus, the coating

formed in the process being removed from the apparatus as a wafer containing the active material.

In a second alternative embodiment of the third aspect of the invention, the coating material is applied onto a substrate, the coating being removed from the substrate as a wafer, for example by a patient prior to the administration of the material. The substrate may be, for example, a sheet comprising plastics material, for example low adhesion plastics material.

The surface substrate may be precoated with one or more coating layers.

Advantageously, the active coating material is applied to a part of a surface of the substrate, the active coating layer forming a first active coated region on the surface of the substrate. Where, for example, a plurality of coating layers are to be applied to each substrate, each coating layer forms a coated region on a part of the substrate.

Thus the method may include the further step of applying a second active coating layer onto a surface of the substrate, the second active coating layer forming a second active coated region on a surface of the substrate.

Preferably, the method further includes the step of applying a cover coating material onto the active coating layer to form a cover coating layer such that the active coating layer is substantially completely covered by the cover coating layer and such that the cover coating layer

is removable from the substrate. Depending on the nature of the cover coating material, the cover coating layer may be removable together with the active coating layer or may be removable separately. The cover coating provides a cosmetic coating and may also protect the active coating material. The cover coating material may also include active material which may be the same as or different from the active material of the active coating layer.

Where more than one active coating layer is applied to the substrate, the method preferably further includes the step of applying a second cover coating layer onto the second active coating layer to form a second cover coating layer such that the second active coating layer is substantially completely covered by the second cover coating layer, the second cover coating layer being substantially separate from the first cover coating layer.

The third aspect of the invention also provides a method of coating a plurality of coating regions onto the surface of a substrate, the method comprising the steps of:

(a) applying active coating material to a surface of the substrate to form a plurality of active coating regions on the surface comprising active coating layers, the active coating material including biologically active material

(b) applying cover coating material to a surface

of the substrate to form a plurality of cover coating regions, the cover coating regions forming layers of cover coating material, each active coating region being substantially completely covered by a cover coating region,

such that each region of active coating and cover coating is removable from the surface of the substrate.

Advantageously, the method further includes the step of removing that active coating layer from the substrate to form a wafer comprising active material. Each wafer may comprise a single dose of active component or a fraction of a dose. Alternatively, the wafer may be subsequently cut to give small wafer units.

Also provided by the third aspect of the present invention is an apparatus for coating a substrate, the apparatus comprising:

(a) a source of coating material

(b) means for moving the substrate relative to the source of coating material,

(c) means for applying an active coating material onto a surface of the substrate to form a plurality of active coating regions,

(d) means for applying a cover coating material onto the surface of the substrate to form a plurality of cover coating regions such that each active coating region is substantially completely covered by a cover coating region,

the coating materials being applied such that the active

coating material is removable from the surface of the substrate.

The third aspect of the invention also provides a coated substrate comprising an active coating layer on a surface of the substrate, the active coating layer including biologically active material and in which the active coating layer is removable from the surface of the coated substrate.

Advantageously, each active coating layer comprises a quantity of biologically active material which is substantially equal to one dose or one half dose of the biologically active material. It will be understood that the quantity of active component will depend on the active material used and the required dose.

Preferably, the substrate further includes a cover coating layer on a surface of the substrate, the cover coating layer substantially completely covering the active coating layer in which the cover coating layer is removable from the surface of the substrate. As indicated above, the cover coating layer may be removable separately from the active coating layer.

The substrate may include a plurality of active coating layers forming active coating regions on a surface of the substrate.

Preferably, each active coating region includes a cover coating region comprising a layer of cover coating material in which each active coating region is substantially completely covered by a cover coating region.

The third aspect of the invention also provides a wafer for administration to a patient, the wafer comprising biologically active material and having a thickness of less than 2mm. Preferably the thickness is less than 1mm.

Embodiments of the invention will now be described by way of example having reference to the drawings of which:

Figure 1 shows schematically a side view of an apparatus for coating a tablet core in accordance with the invention;

Figure 2 shows schematically a side view of a part of the apparatus of Figure 1;

Figure 3 shows schematically a cross sectional view of part of the apparatus of Figure 1; and

Figures 4a to 4c show cross sectional views of tablet cores coated in accordance with the invention.

The apparatus shown in Figure 1 is for coating both faces of pharmaceutical tablet cores. The apparatus comprises an inclined tablet core feed chute 1 leading to a first rotatable wheel 2 having circular depressions 3 in its outer surface. The cores 4 are fed from the chute 1 into the depressions 3 where they are held by suction by means of a suction line 5 in communication with the

base of the depression 3 via an opening. The first drum is rotated in the direction shown by the arrow A. Adjacent to the outer surface of the wheel 2 downstream from the feed chute 1 is an active coating station 6 and a cover coating station 7. Downstream from the active coating station is an active coating fusing station 8 at which the active coating is fused and downstream from the cover coating station 7 is a cover coating fusing station 9 at which the cover coating is fused. A cooling station (not shown) may be provided downstream from each of the fusing stations 8, 9 where cool air is directed at the core to cool the fused coating.

A second wheel 10 similar to the first wheel 2 is arranged adjacent to the first wheel 2, the nip between the wheels being downstream of the fusing station 9. The second wheel 10 rotates in an opposite sense to that of the first wheel 2 as shown by the arrow B. Arranged adjacent to the outer edge of the second wheel 10 downstream from the nip of the two wheels are a second cover coating station 11 and a second fusing station 12.

The tablet cores are fed continuously from the core feed chute 1 to the depressions 3 in the rotating wheel 2. The core lies over the opening in the depression 3 leading to the suction line 5 and the core is held in the depression by suction. The core is moved on the rotating wheel 2 to the active coating station 6 where active coating including biologically active material is applied as described in more detail below and is fused at

the active coating fusing station 8. The core then moves to the cover coating station 7 where a further coating is applied over the active coating. The coated core then moves to the fusing station 9 where a heater fuses the cover coating to form a film coating secured to the core.

When the core in the depression 3 reaches the nip between the two wheels, the suction holding the core in the depression 3 is released and the core is transferred into a depression 3′ on the surface of the rotating second wheel 10 where it is held by suction with coated surfaces of the core adjacent to the surfaces of the depression and the uncoated surfaces of the tablet exposed.

The second wheel 10 moves the core to the second cover coating station 11 and the second fusing station 12 and a second cooling station (not shown) to form a fully coated tablet core.

The core is then moved to an exit chute 1′. The suction holding the core is released and the core drops from the wheel along the chute which takes the cores to be further processed and/or packed.

It will be understood that where only one face of the tablet core is to be coated, the second wheel 10 would be omitted. Further, where an active coating of material including biologically active material is to be coated onto both faces of the tablet, a further active coating station 6′ would be positioned by the second wheel upstream from the second cover coating station.

It will be appreciated that the coating material in each of the two cover coating stations may be the same or different materials, and where more than one active coating station is used, the coating material in each of the active coating stations may be the same or different materials.

Figure 2 shows the active coating device 6 in more detail. Figure 2 shows a portion of the wheel 2 together with a core 4 in a depression 3 on the surface of the wheel 2.

The active coating station 6 comprises a conveyor 13 arranged in a loop in a vertical plane so that the upper surface 14 faces the surface of the wheel and the cores 4 which pass the device 6 as the wheel rotates. The contour of the upper surface 14 of the conveyor 13 is chosen to match the contour of the outer surface of the wheel so that the distance between the core and the upper surface of the conveyor is unchanged as the wheel rotates. The direction of rotation C of the conveyor 13 is such that the direction of movement of the upper surface of the conveyor is opposite to that of the movement of the core over the upper surface of the conveyor.

As shown in Figure 2, a corona charge wire 15 and a powder source 16 are arranged beneath the conveyor immediately below the lower surface 17 of the conveyor.

The corona charge wire 15 sprays charge onto the lower surface 17 of the conveyor. It will be appreciated

that a different method could be used to apply charge to the conveyor.

The powder source 16 uses an archimedes screw to form a small mound of powder beneath the lower surface of the conveyor. The source 16 comprises a hopper 18 containing the powder including the biologically active component, and an Archimedes screw 19 which in use passes through the powder material 20 in the hopper 18 and through a vertical barrel 21. Thus, the powder material 20 is circulated from the lower regions of the hopper 18 to the top of the barrel 21 where a moving heap of powder is formed. The heap will be of substantially constant size and shape as excess powder overflows from the top of the barrel 21 and is returned to the hopper 18.

Stirrers 22 are provided in the hopper 18 to help to improve the flow of the powder and break up any agglomerates.

Thus a small moving heap of powder of substantially constant size and shape is formed beneath the lower surface of the conveyor 17.

It will be appreciated that a device other than the Archimedes screw could be used to form the heap of powder.

The powder source 16 is located downstream from the charge spraying device 15 and powder from the heap of powder is attracted to the surface of the charged conveyor 17 where it forms a thin, uniform layer which is transported to the upper surface 14 of the conveyor.

The tablet core 4 passing over the upper surface of the conveyor is held at a different potential from that of the conveyor 13, either by earthing the core or applying a charge to the core as described below, and powder on the conveyor moves from the conveyor to the exposed surfaces of the tablet core 4 to form a powder coating.

The active coating station 6 is enclosed in a housing (not shown) to reduce the risk of powder loss of the active powder. In use the housing has an opening above the upper surface of the conveyor 14 so that the tablet core 4 is exposed to the active powder coating material as it passes the station 6.

It will be appreciated that the thickness of the powder layer formed on the surface of the tablet core depends on several factors including the amount of charge sprayed onto the conveyor, the magnitude of the charge applied to the core, the size of the heap of powder produced, the size of the opening in the housing and the speed of the conveyor. Those factors will be varied to give the desired coating depending on the type of powder and core used.

The tablet core including the active coating then passes to the active coating fusing station 8 which comprises a heater which is used to fuse the coating material. A cooler situated downstream from the active coating fusing station 8 directs air at the core to cool the fused active coating.

The active coated tablet core then passes to the cover coating station 7 where a charge is applied to the tablet core as described below and the core is passed over an earthed trough containing the cover coating powder. The powder from the trough is attracted to the exposed surfaces of the tablet core to form a cover coating over the active coating. The tablet then passes to the cover coating fusing station 9 where the cover coating is fused to form a film coating and to a cooling station where cool air is directed at the core to cool the fused coating.

As shown in Figure 3, where a charge is to be applied to the tablet core at one or more of the coating stations, each depression 3 is electrically insulated from the other depressions on the wheel by means of a cup of insulating material 23 and is provided with a respective pick up arm 24 extending radially inward from the depression 3 towards but ending short of the centre of the wheel. The pick up arms 24 are attached to the inner surface of the wheel 2 and rotate with it. Each associated pick up arm 24 and depression 3 together make a moving electrode which is in contact with the core 4 when it is located in the depression 3.

A stationary electrode 25 is located inside the wheel at each angular position corresponding to each coating station, as required. The outer surfaces of the stationary electrodes are at the same radial distance from the centre of the wheel as the free ends of the pick

up arms 24 of the moving electrodes. As the wheel 2 rotates, the moving electrodes contact the stationary electrodes and a charge is applied to the tablet core 4 in the depression 3.

The partially coated tablet core then passes onto the second wheel, and the uncoated surfaces are coated with a cover coating in a similar way.

Figures 4a and 4b show schematic cross-sectional views of tablets coated in accordance with the first aspect of the present invention. The tablet shown in Figure 4a comprises a core 4, an active coating layer 26 comprising active material covering the upper surface and part of the side surface of the core, and a cover coating 27 covering the active coating layer 26. The core also has a further cover coating 28 covering the opposite face and part of the side surface of the core. The further cover coating 28 may be of the same or different composition as that of the cover coating 27.

It will be appreciated that the thickness of the coating layers relative to the size of the core have been greatly exaggerated for clarity. For a tablet core of thickness 5mm, the thickness of each coating layer would usually be of the order of from 5 to 100μm.

Where the apparatus described above is used to coat the cores, most of the coating material deposited on the core surface will be deposited on the face of the core facing the powder source such that the coating on that face of the core will be thicker than the coating on the

exposed side faces of the core where less coating material is deposited.

Figure 4b shows a tablet having an active coating 26' and a cover coating 27'. The tablet is similar to that of Figure 4a except that there is no further cover coating on the opposite side of the core.

It will be appreciated that tablets having other combinations of active coatings and cover coatings could be produced.

The composition of the active coating material used will of course depend on the active ingredient to be used and the amount of the coating to be applied.

Active materials most suitable to be applied to the tablet include those materials having a high therapeutic activity, for example those where the usual prescribed dose is about 1mg or less, and which have a good stability to degradation due to heat where the coating material containing active material is to be heated.

An active material which may be applied to a tablet core in accordance with the invention is Diltiazem HCL.

The amount of active ingredient to be coated onto each core will generally be small and the active ingredient will usually be diluted with one or more excipients. The excipients used will be chosen so that they aid the coating of the active material onto the cores by, for example improving the electrostatic properties of the powder and its physical properties and aiding the formation of the fused active coating, for

example the excipient may be a material which melts at a low temperature to aid the formation of a film.

Where the active coating material is a powder, the particle size will be an important factor with regard to the transfer of the active coating material from the conveyor to the tablet core and to the subsequent fusing of the material. Usually a particle size range of 1 to 200μm will be used (at least 90% of the particles of the powder having a size within that range).

One example of an active coating material is as follows:

Xylitol	45% wt
Diltiazem HCL (active)	45% wt
TiO_2	9% wt
Colloidal silica	1% wt

It is thought that in at least one embodiment of the invention, the active composition will comprise three main components together with additives.

The components may, for example, comprise the following

i) a film forming excipient, for example Xylitol or PEG 6000,

ii) the active component,

iii) a particle seed and/or charge modifying component, for example TiO_2 or silica,

iv) a flow aid, for example colloidal silica or magnesium stearate.

Each component may comprise one or more different

materials.

The active coating material of the above example was in the form of a powder and had a particle size distribution such that at least 90% wt of the particles had a size in the range of from 5 to 25μm.

The active powder coating material may be produced using one or a combination of the following processing steps:

a) precipitation of two or more of the components to form composite particles

b) spray drying of two or more of the components to form composite particles

c) granulation

d) micronisation.

For example, all of the components of the composition may be co-micronised to give a powder material having the desired particle size.

An example of a powder cover coating material is as follows:

39.75%	Eudragit RS (ammonio-methacrylate copolymer)
39.75%	Klucel (hydroxy propyl cellulose)
15.0%	Titanium dioxide
5.0%	Aluminium lake
0.5%	Aerosil 200 (colloidal silicon dioxide)

The cover coating material was prepared by the

following method:

a) A sample containing the % wt of components listed above was premixed in a high shear mixer. Water was added to the mixture in a high shear mixer for a few minutes to give a granulated mixture which was dried in a fluid bed drier at a temperature of about 45°C for 20 to 30 minutes to give a material having a moisture content (measured as loss on drying) below 3% by weight. The material was impact milled and then micronised using a fluid energy mill to a powder containing particles having a size distribution such that 50% by volume of particles were of a size less than 20μm.

The cover coating material will usually include components to control the dissolution rate of the cover coating to give controlled release of the active material in the active coating layer. Where more than one active coating is applied to each tablet, the release of each active coating can be different where different materials are used for the cover coating over each of those active coatings.

Where one or more of the coatings are applied as liquid coatings, a suitable liquid coating device would be used at the active coating station 6 and/or the cover coating station 7 and the fusing device would be replaced by, for example a drying device to dry the liquid coating, if necessary.

In an embodiment according to the second aspect of the invention, an apparatus similar to that described

above and as shown in Figures 1 and 3 is used to coat pharmaceutical tablet cores.

At the active coating station 6, active coating material in the form of a liquid is applied to a surface of a pharmaceutical tablet core held on the first wheel 2. A head for applying the liquid is positioned such that the outlet or outlets of the head is less than 1mm from a surface of a tablet core held on the wheel 2 at the active coating station 6.

The head may be an ink jet printer head, for example an adapted Compact 200 head manufactured by Alphadot Limited. That head has 5 outlets spread over an area of about 10mm and can be used to direct liquid coating material towards the exposed surfaces of the tablet core such that, for a tablet core having two parallel flat faces, the liquid coating substantially completely covers one of the flat faces.

The liquid coating material comprises the active component and a solvent, preferably water, and an excipient, for example PEG, to aid in film forming. Preferably the solids content of the liquid coating material is very low, advantageously there would be substantially no solids content and advantageously the active material is fully dissolved in the solvent.

Examples of active liquid coating materials which may be used are as follows

a)	Sodium citrate	0.02
	Chlorpheniramine maleate	2.48
	Propylene glycol	4.00
	Water	18.50
	Ethanol	75.00
b)	Sodium citrate	0.02
	Chlorpheniramine maleate	2.00
	Methocel E15	1.00
	Lactose B.P.	6.00
	PEG 4000	1.00
	Water	89.98

The amounts given above represent percentage by weight of each component.

The apparatus may include heating means 8 downstream from the coating station 6 for drying the applied coating material. However, where the liquid coating material is such that the solvent evaporates quickly, the heater 8 may not be required. It will be appreciated that where the heater 8 is used the temperature required to dry the active coating will be significantly lower than the temperature required to fuse powder coating material as described above.

The apparatus may further include a cover coating station 7 and a fusing station 9 as described above and, where the core is to be further coated, the apparatus includes a second wheel 10 with a coating station 11 and fusing station 12 as described above. Where a further

active coating is to be applied, a further active coating station and, optionally, a further heater may be provided upstream from the coating station 11. An example of a suitable cover coating material is given in respect of the first aspect of the invention described above.

Figure 4c shows a tablet coated by a method in accordance with the second aspect of the invention. The tablet comprises a core 4, a first active coating layer 26'' covering substantially all of the upper face of the core, a cover coating 27'' covering the active coating layer and part of the sides of the tablet core, a second active coating layer 29 covering part of the lower surface of the core and a second cover coating layer 28 covering the second active coating layer 29. The two active coating layers 26'' and 29 may include the same or different active ingredients; the two cover coating layers 27'' and 28 may be of the same or different material and may have different dissolution rates.

Where the active coating material is applied using the method described above, substantially all of the coating material is applied to a face of the tablet core, with substantially no coating material being applied to the sides of the tablet core.

In an embodiment of the third aspect of the invention an apparatus similar to that shown in Figure 2 is used to form wafers of coating material.

The apparatus comprises a conveyor belt of chemically inert material having a Teflon (RTM) coating.

A corona charge wire is arranged immediately below the lower surface of the conveyor and sprays charge onto the lower surface. A powder source similar to that shown in Figure 2 is also arranged beneath the lower surface of the conveyor downstream of the corona wire. The powder material in the powder source contains an active component and may have similar composition to the active powder described above in relation to the first aspect of the invention. Preferably a higher proportion of film-forming components are added to the powder, for example hydroxypropylcellulose (HPC).

An example of an active coating material is as follows:

Eudragit RS	23%
Diltiazem HCL (active)	40%
HPC	25%
TiO_2	7%
PEG 4000	5%

The amounts of the components are expressed as percent by weight.

Powder from the powder source is attracted to the surface of the charged conveyor where it forms a thin, uniform layer of powder on a part of the outer surface of the conveyor belt. A heater is positioned downstream of the powder source and the heater fuses the powder material on the conveyor surface to form a fused film

coating on the surface. The film coating is conveyed on the conveyor to a region where it is removed as a thin strip of film.

A cooling station may be positioned downstream of the heater to cool the film coating. The film strip removed from the conveyor may be passed to a cutting station where it is divided into portions, each of which may contain a dose of active material.

In an alternative embodiment of the third aspect of the invention, powder material is deposited onto a tape, preferably of plastics material.

Claims

1. A method of coating a pharmaceutical substrate, the method including the steps of:

(a) applying an active coating material to a surface of the substrate to form an active coating layer, the active coating material comprising biologically active material and

(b) applying a cover coating material onto the active coating layer to form a cover coating layer such that the active coating layer is substantially completely covered by the cover coating layer.

2. A method according to claim 1, wherein the active coating material is applied electrostatically.

3. A method according to claim 1 or claim 2, wherein the active coating material is applied in the form of a dry powder.

4. A method according to claim 3, wherein at least 90% by weight of the particles of the active coating material have a particle size between from 1 to 200μm.

5. A method according to any preceding claim, wherein the active coating material further includes one or more excipients.

6. A method according to any preceding claim, wherein the substrate is supported on a support means during the coating of the active coating material.

7. A method according to 6, wherein the support means conveys the substrate through a region adjacent to a source of the active coating material.

8. A method according to claim 6 or claim 7, wherein the method comprises supporting the substrate adjacent to the source of the active coating material with a surface of the substrate maintained at such a different electric potential from that of the active coating material that the application of the electric potential causes the active coating material to move from the source of the active coating material towards the substrate, a surface of the substrate becoming coated with the active coating material.

9. A method according to any of claims 6 to 8, wherein the substrate is supported from above and the powder moves from the source upwards towards a lower surface of the substrate.

10. A method according to any of claims 6 to 9, wherein the substrate is charged when the substrate is adjacent to the source of the active coating material.

11. A method according to any of claims 6 to 10, wherein the source of active coating material is charged.

12. A method according to any preceding claim, wherein the method further includes the step that after the active coating layer is applied the active coating material is treated to form an active film coating secured to the surface of the substrate.

13. A method according to any preceding claim, wherein the cover coating material is applied electrostatically.

14. A method according to any preceding claim, wherein the cover coating material is in the form of a powder.

15. A method according to claim 14, wherein at least 90% by weight of the particles of the cover coating material have a particle size between from 1 to 200μm.

16. A method according to any preceding claim, wherein the substrate is supported on a support means during the coating of the cover coating material.

17. A method according to claim 16, wherein the support means conveys the substrate through a region adjacent to a source of the cover coating material.

18. A method according to claim 16 or claim 17, wherein the method comprises supporting the substrate adjacent to the source of the cover coating material with a surface of the substrate maintained at such a different electric potential from that of the cover coating material that the application of the electric potential causes the cover coating material to move from the source of the cover coating material towards the substrate, a surface of the substrate becoming coated with the cover coating material.

19. A method according to any of claims 16 to 18, wherein the substrate is supported from above and the powder moves from the source upwards towards a lower surface of the substrate.

20. A method according to any of claims 16 to 19, wherein the substrate is charged when the substrate is adjacent the source of the cover coating material.

21. A method according to any of claims 16 to 20, wherein the source of cover coating material is charged.

22. A method according to any preceding claim, wherein the method further includes the step that after the cover coating layer is applied the cover coating material is treated to form a film coating secured to the surface of the substrate.

23. A method according to any preceding claim, wherein the active coating layer covers only part of a surface of the substrate.

24. A method according to claim 23, wherein the cover coating layer covers only part of a surface of the substrate.

25. A method according to any preceding claim, wherein the method further includes the step of applying a further coating material to a surface of the substrate to form a further coating layer.

26. A method according to claim 25, wherein the further coating material includes biologically active material, the further coating layer forming a further active coating layer.

27. A method according to claim 26, wherein the method further includes the step of applying a further cover coating material onto the further active coating layer to form a further cover coating layer such that the further active coating layer is substantially completely covered by the further cover coating layer.

28. A method according to any preceding claim, wherein the method is continuous.

29. A method according to any preceding claim, wherein

the coated pharmaceutical substrate is a solid dosage form.

30. A method according to claim 29, wherein the quantity of active coating material in the active coating layer is substantially equal to a dose of the active material.

31. Apparatus for coating a pharmaceutical substrate according to a method as claimed in any of claims 1 to 30.

32. An apparatus for coating a pharmaceutical substrate, the apparatus comprising:

(a) a source of active coating material,

(b) support means for supporting a substrate adjacent to the source of the active coating material such that the active coating material forms an active coating layer on a surface of the substrate,

(c) a source of a cover coating material,

(d) means for conveying the substrate having the active coating layer to a position adjacent to the source of cover coating material such that the cover coating material forms a cover coating layer which substantially completely covers the active coating layer.

33. An apparatus according to claim 32, wherein the source of active coating material comprises a conveyor for conveying active coating material through a region in which the substrate is supported by the support means.

34. An apparatus according to claim 33, further including means for supplying active coating material to the source, the supplying means comprising a

reservoir of active coating material arranged adjacent to the conveyor, and means for transferring the active coating material from the reservoir to the conveyor.

35. An apparatus according to claim 34, wherein the means for transferring the active coating material includes charging means for applying a charge to the conveyor.

36. An apparatus according to claim 34 or claim 35 wherein the reservoir is arranged below the conveyor.

37. A pharmaceutical product comprising a substrate, an active coating layer on a surface of the substrate, the active coating layer comprising biologically active material, and a cover coating layer substantially completely covering the active coating layer.

38. A pharmaceutical product according to claim 37, further including a second active coating layer, and a cover coating layer substantially completely covering the second active coating layer.

39. A pharmaceutical product according to claim 37 or claim 38, wherein the cover coating layer covering the first active coating layer is different from the cover coating layer covering the second active coating layer.

40. A pharmaceutical product according to any of claims 37 to 39, wherein the product is a solid dosage form.

41. A pharmaceutical product according to any of

claims 37 to 40, wherein the substrate contains biologically active material.

42. A pharmaceutical product made by a method according to any of claims 1 to 30.

43. A method of coating a pharmaceutical substrate, the method including the step of applying a metered dose of an active coating material to a surface of the substrate, to form an active coating layer on the surface, the active coating material comprising biologically active material.

44. A method according to claim 43, wherein the active coating material is applied in the form of a liquid.

45. A method according to claim 44, wherein a predetermined number of droplets of active coating material are applied to the surface of the substrate.

46. A method of coating pharmaceutical substrates, the method including the step of applying a quantity of an active coating material to a surface of each substrate, to form an active coating layer, the active coating material including biologically active material, the method being such that the coefficient of variation of the quantity applied to each substrate is not more than 15%.

47. A method according to claim 46, wherein the coefficient of variation is not more than 10%.

48. A method of coating a pharmaceutical substrate, the method including the step of applying active

coating material from a supply to a surface of the substrate to form an active coating layer, the active material comprising biologically active material, wherein the active coating material is applied in the form of individual liquid droplets which are propelled from the supply directly towards a surface of the substrate.

49. A method of coating pharmaceutical substrates, the method including the step of applying active coating material from a supply to a surface of each of the substrates to form an active coating on each substrate, the active material comprising biologically active material, wherein substantially all of the active coating material released from the supply is applied to a surface of a substrate.

50. The use of an ink jet head in the coating of pharmaceutical substrates with active coating material, the active coating material comprising biologically active material.

51. A method of coating a pharmaceutical substrate, the method including the step of applying an active coating material to a surface of the substrate to form a coating layer, the active coating material comprising biologically active material, in which the area of the surface of the substrate covered by the active coating layer is less than 40% of the total surface area of the substrate.

52. A method of coating a pharmaceutical substrate,

the method including the step of applying an active coating material to an exposed surface of the substrate to form an active coating layer, the active coating material comprising biologically active material, in which the coating layer covers only a part of the exposed surface of the substrate.

53. A method according to claim 51 or claim 52, wherein the area of the exposed surface covered by the active coating layer is less than 10% of the total area of the exposed surface.

54. A method according to any of claims 51 to 53, wherein the coating material is applied in the form of a jet of liquid droplets directed at an exposed surface of the substrate.

55. A method according to any of claims 43 to 54, wherein the coated pharmaceutical substrate is a solid dosage form.

56. A method according to any of claims 43 to 55, wherein the active coating material is applied electrostatically.

57. A method according to any of claims 43 to 56, the method further including the step of applying cover coating material to the surface of the substrate to form a cover coating layer such that the active coating layer is substantially completely covered by the cover coating layer.

58. A method of coating a pharmaceutical substrate, the method including the step of applying an active

coating material to a surface of the substrate to form an active coating layer, the active coating material comprising biologically active material, the active coating material being applied in the form of a jet of particles of coating material.

59. An apparatus for coating a pharmaceutical substrate, the apparatus comprising

(a) a source of active coating material, the active coating material comprising biologically active material,

(b) support means for supporting the substrate adjacent the source of active coating material

wherein the source comprises means for applying a metered dose of active coating material on a surface of the substrate.

60. An apparatus for coating a pharmaceutical substrate, the apparatus comprising

(a) a source of active coating material, the active coating material comprising biologically active material,

(b) support means for supporting the substrate adjacent the source of active coating material

wherein the source comprises an ink jet head.

61. An apparatus for coating a pharmaceutical substrate, the apparatus comprising

(a) a source of active coating material, the

active coating material comprising biologically active material,

(b) support means for supporting the substrate adjacent the source of active coating material

wherein the source comprises means for directing droplets of liquid active coating material towards a surface of the substrate.

62. An apparatus for coating a pharmaceutical substrate, the apparatus comprising

(a) a source of active coating material, the active coating material comprising biologically active material,

(b) support means for supporting the substrate adjacent the source of active coating material

(c) means for applying active coating material from the source onto a surface of the substrate to form a layer of coating material on the surface of the substrate such that the area of the surface covered by the coating layer is less than 25% of the total surface area of the substrate.

63. An apparatus according to any of claims 59 to 62, wherein the means for applying the coating material includes means for directing coating material onto the surface of the substrate in the form of a jet of liquid droplets.

64. An apparatus according to any of claims 59 to 63,

wherein the apparatus further includes means for applying a cover coating material onto the surface of the substrate to form a cover coating layer such that the cover coating material layer substantially completely covers the active coating layer.

65. An apparatus for a method according to any of claims 51 to 58.

66. A pharmaceutical product comprising a substrate and an active coating layer covering less than 25% of the surface area of the substrate, the active coating layer comprising biologically active material.

67. A pharmaceutical product according to claim 66, further comprising a cover coating layer substantially completely covering the active coating layer.

68. A pharmaceutical product made by a method according to any of claims 51 to 58.

69. A pharmaceutical product according to any of claims 66 to 68, wherein the product is a solid dosage form.

70. A method of coating a substrate, the method including the steps of applying an active coating material to a surface of the substrate to form an active coating layer, the active coating material comprising biologically active material, wherein the active coating layer is removable from the substrate.

71. A method according to claim 70, wherein the active coating material is applied electrostatically.

72. A method according to claim 70 to 71, wherein the

active coating material is applied in the form of a dry powder.

73. A method according to any of claims 70 to 72, wherein the active coating material is applied to a part of a surface of the substrate, the active coating layer forming a first active coated region on the surface of the substrate.

74. A method according to any of claims 70 to 73, wherein the method further includes the step of applying a cover coating material onto the active coating layer to form a cover coating layer such that the active coating layer is substantially completely covered by the cover coating layer and such that the cover coating layer is removable from the substrate.

75. A method according to any of claims 70 to 74, wherein the method includes the further step of applying a second active coating layer onto a surface of the substrate, the second active coating layer forming a second active coated region on a surface of the substrate.

76. A method according to claim 75, wherein the method further includes the step of applying a second cover coating layer onto the second active coating layer to form a second cover coating layer such that the second active coating layer is substantially completely covered by the second cover coating layer, the second cover coating layer being substantially separate from the first cover coating layer.

77. A method of coating a plurality of coating regions onto the surface of a substrate, the method comprising the steps of:

(a) applying active coating material to a surface of the substrate to form a plurality of active coating regions on the surface comprising active coating layers, the active coating material including biologically active material

(b) applying cover coating material to a surface of the substrate to form a plurality of cover coating regions, the cover coating regions forming layers of cover coating material, each active coating region being substantially completely covered by a cover coating region,

such that each region of active coating and cover coating is removable from the surface of the substrate.

78. A method according to any of claims 70 to 77, the method further including the step of removing the active coating layer from the substrate to form a wafer comprising active material.

79. An apparatus for coating a substrate, the apparatus comprising:

(a) a source of coating material

(b) means for moving the substrate relative to the source of coating material,

(c) means for applying an active coating material onto a surface of the substrate to form a

plurality of active coating regions

(d) means for applying a cover coating material onto the surface of the substrate to form a plurality of cover coating regions such that each active coating region is substantially completely covered by a cover coating region,

the coating materials being applied such that the active coating material is removable from the surface of the substrate.

80. A coated substrate comprising an active coating layer on a surface of the substrate, the active coating layer including biologically active material and in which the active coating layer is removable from the surface of the coated substrate.

81. A coated substrate according to claim 80, the substrate further including a cover coating layer on a surface of the substrate, the cover coating layer substantially completely covering the active coating layer in which the cover coating layer is removable from the surface of the substrate.

82. A coated substrate according to claim 80 or claim 81, wherein the substrate includes a plurality of active coating layers forming active coating regions on a surface of the substrate.

83. A coated substrate according to claim 82, wherein each active coating region includes a cover coating region comprising a layer of cover coating material in which each active coating region is substantially

completely covered by a cover coating region.

84. A coated substrate when made according to a method as claimed in claims 70 to 78.

85. A wafer for administration to a patient, the wafer comprising biologically active material and having a thickness of less than 2mm.

86. A wafer produced by a method according to claim 78.

87. A method substantially as herein described having reference to Figures 1, 2, 3 and 4a to 4c.

88. An apparatus substantially are herein described having reference to Figures 1, 2, 3 and 4a to 4c.

89. A coated pharmaceutical substrate substantially as herein described having reference to Figures 1, 2, 3 and 4a to 4c.

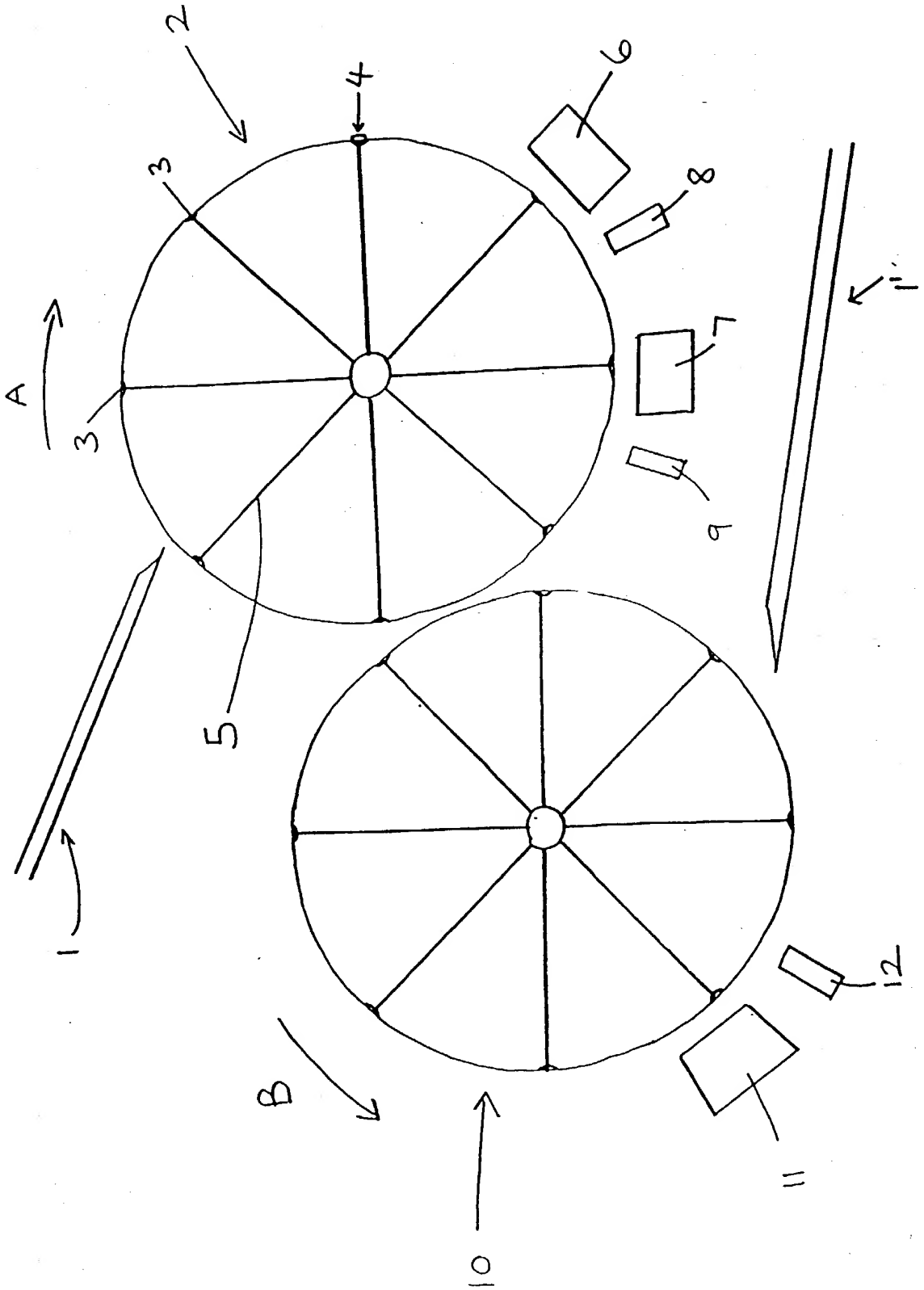


Fig. 1

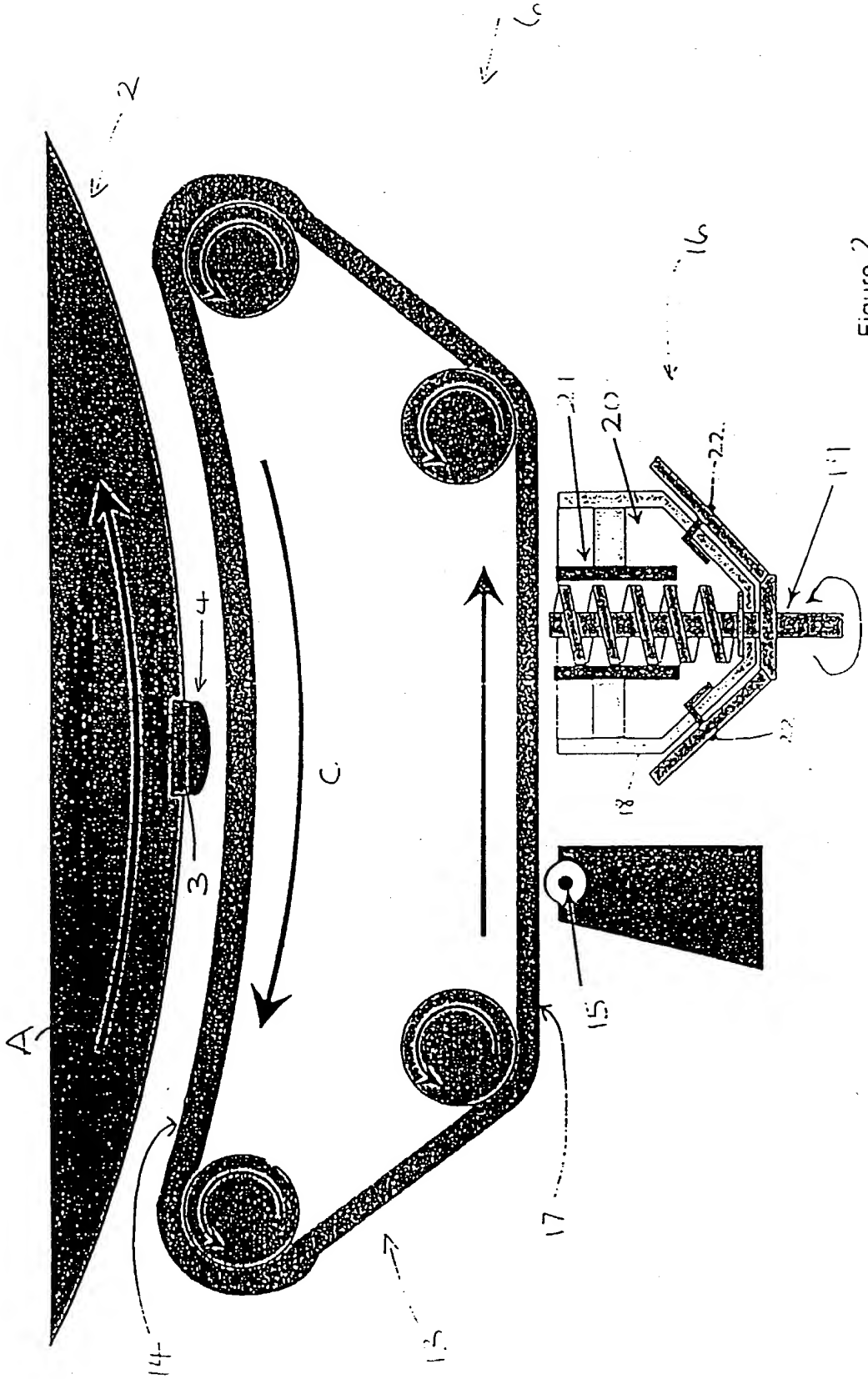
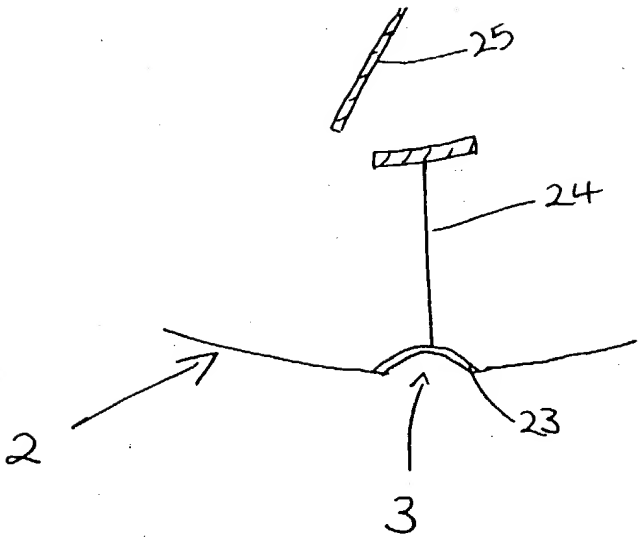


Figure 2



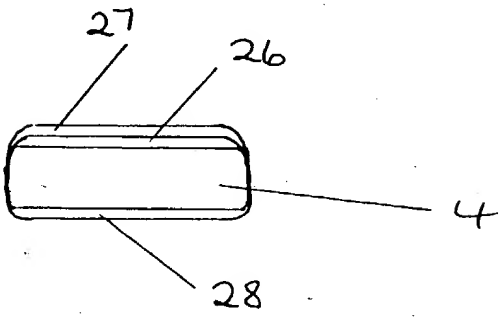


Fig 4a

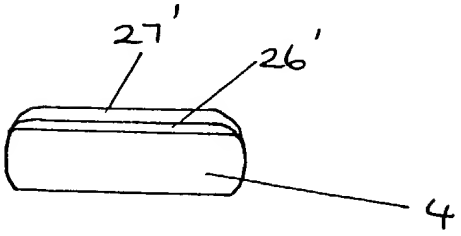


Fig. 4b

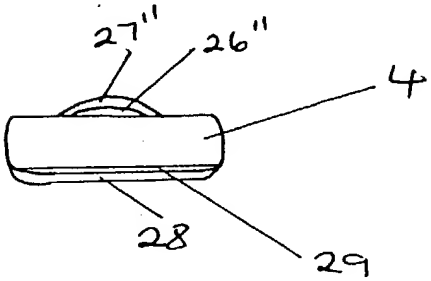


Fig 4c.